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PREDICTORS OF ON-TREATMENT MORTALITY OF PATIENTS UNDERGOING PALLIATIVE RADIATION THERAPY: IMPROVING THE QUALITY OF END-OF-LIFE CANCER CARE

Matthew Stephen Ning
UTHealth School of Public Health

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by

DR. MATTHEW S. NING, MD

APPROVED:

Rebecca Wells

DR. REBECCA WELLS, PHD, MHSA

Rebecca Wells

DR. REBECCA WELLS, PHD, MHSA

MD, PhD

DR. MARY FRANCES MCALEER, MD, PHD

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MATTHEW STEPHEN NING

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Matthew Stephen Ning, MD, MPH

The University of Texas

School of Public Health, 2019

CE/Thesis Chair: Dr. Rebecca Wells, PhD, MHSA

ABSTRACT

PURPOSE: Excessive medical treatment at end-of-life is an indicator of poor quality care. While radiation therapy (RT) is effective for palliation, some patients die shortly after or even during treatment. Any treatment that requires terminal patients to spend significant time in the hospital setting contradicts palliative goals. This study investigates patterns of end-of-life RT to inform quality improvement initiatives.

METHODS: All patients who died within 6 months of starting RT at a single large academic cancer center between 2015 through 2018 were identified through our institutional databases on an Institutional Review Board-approved protocol. Clinical factors including age, treatment service, number of fractions, diagnosis, treatment site, and treatment date were evaluated for associations with endpoints, 30-day mortality and on-treatment mortality (mid-course), via logistic regression analysis.

RESULTS: 1,855 patients died within 6 months of initiating RT at our center. Of these, 619 patients (33%) died within 30 days of starting RT, and were most commonly treated by thoracic (26%), CNS (21%), and hematologic (13%) services. Commonly treated sites included brain/spine (27%), bone (26%), and mediastinum/thorax (10%). On logistic regression, both extended radiotherapy prescription fractionation (>10 fractions/course) [OR 0.50, p<0.001] and advanced stereotactic treatment technique (OR 0.61, p=0.002) were associated with decreased likelihood of 30-day mortality, reflecting appropriate clinical rationale of treating providers. Neither age (≥70 vs. <70 years) [OR 0.93, p=0.538] nor treatment year (2017-2018 vs. 2015-2016) [OR 0.97, p=0.744] were associated with 30-day mortality. Of the 619 patients, 142 (23%) died midway before completion of RT course. Patients treated for emergent palliative mediastinal/thoracic indications (OR 11.4, p<0.001) were more likely to die midway through RT than those treated for bone metastases. Notably, 2 out of every 3 patients treated for emergent palliative mediastinal/thoracic indications (e.g. airway obstruction, hemoptysis) died on-treatment, comprising 27% of all on-treatment deaths (p<0.001).

CONCLUSION: Palliative RT remains an important therapeutic tool at the end-of-life. However, careful consideration of RT for emergent mediastinal/thoracic indications should be used, given the high potential for on-treatment mortality. Taken together, these data may help inform physician decision-making and facilitate treatment consistent with palliative goals at the end-of-life.

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BACKGROUND

Literature Review

Excessive medical treatment at the end-of-life is an indicator of poor quality care [1]. Radiation therapy is routinely used for both curative and palliative cancer treatment. Radiation can be an effective tool for palliation of symptoms arising from cancer, such as pain from bone metastases or neurologic compromise from brain or spinal metastases.

Although radiation is often well-tolerated with good outcomes, regardless of goals of therapy, there are some patients that die soon after or even during treatment. Furthermore, any treatment that requires dying patients to spend a significant proportion of their final days in a hospital is contrary to the overall aims of palliative care.

Nationwide, it is estimated that the majority of overall healthcare costs may be attributed to care for patients within their last year of life [1-3]. Contributing to this empirical pattern is the statistic that 1 in 5 patients who received radiation in their final 30 days of life spend more than 10 of those days receiving treatment [1]. In addition, among these patients, there has been a shift towards more advanced radiation technologies, away from simpler (and most cost-effective) techniques [2-3].

These factors contribute to the finding that the costs of care for patients who received radiotherapy at the end of life are higher than for those patients who did not

[1]. Taken altogether, there is a need for quality improvement initiatives related to palliative radiation delivered at the end-of-life.

Public Health Significance

As previously mentioned, there is a need for additional research into appropriate indications for radiation at the end-of-life, to facilitate physician decision-making regarding use of radiation consistent with palliative goals for patients with end-stage cancer. For example, clinical guidelines could help oncologists reconsider treatment or offer shorter (lower cost) treatment courses for uncomplicated cases while still maintaining quality-of-life for such patients.

From a healthcare value framework, by defining indications for palliative radiation (and reducing utilization in these scenarios), such guidelines would promote the Institute for Healthcare Improvement (IHI) quality dimensions of effectiveness, patient-centeredness, and safety (as some patients may have hastened death due to excessive treatment courses). Furthermore, these guidelines would be disseminated via publication to promote quality improvement on a national population level.

Specific Research Aims and Objectives

In this study, we are first interested in quantitatively analyzing our collective experience (as the largest national cancer center) in treating patients to identify any

predictors of mortality in patients that are treated with radiation therapy, so that we can better select optimal treatments in the future and provide quality care. Data from this initial quantitative analysis will then be applied towards the following aims and objectives related to the field of public health, which require a more comprehensive interpretation in the context of the current literature:

1. By identifying recurring themes in these cases (particularly for patients who die in-hospital away from their homes midway through treatment), these findings would serve as a sort of immediate **quality improvement initiative** for our Department of Radiation Oncology-- to communicate appropriate indications to our 70 Radiation Oncology attending providers on the frontlines of oncological care, defining those specific settings in which they should exercise particular caution in deciding whether or not to offer treatment. With such guidelines, we would expect to see these on-treatment mortality rates decrease (as well as the overall numbers of patients getting aggressive treatments at the end-of-life).

2. We would then **communicate these guidelines/criteria via publication**, for other providers across the country to refer to and apply within their Departments, **in an effort to improve healthcare quality on a national population level**.

3. Finally, we will **interpret these findings from the perspective of a healthcare value framework**. If these treatments are prescribed gratuitously, they provide questionable benefit in terms of patient comfort and quality-of-life. Furthermore, they are associated with sometimes high absolute healthcare costs to the patient/payer and provider, making them relatively low-value treatments. Although cost-specific analyses are beyond the scope of this study, by defining less-than-appropriate indications for palliative radiation (and reduce utilization in these scenarios), we would promote the IHI healthcare quality dimensions of effectiveness, patient-centeredness, and even safety (as some patients may have hastened death due to "aggressive" treatment courses).

METHODS

Study Design

In the initial quantitative data-generation portion of this study, the hospital and radiation therapy charts of individual patients treated with radiation therapy (with both curative and palliative intent) were reviewed and correlated to time of death. Patients who died within 6 months of starting radiation therapy, including those treated with definitive (curative) intent and those undergoing palliative treatment were identified through the institutional database.

Once the cohort was established, individual clinical variables (e.g. age, diagnosis, treatment site, hospitalization status, etc.) were analyzed and used to determine if there was an ability to predict mortality during or after radiation therapy, as per the statistical methods outlined in detail below.

Data from this initial quantitative analysis are being applied towards a more comprehensive review of the data to address the aforementioned research aims and objectives related to public health. Most notably, we will summarize our findings and establish clinical guidelines for other practitioners to improve healthcare quality in the palliative end-of-life setting at a national population level. Furthermore, we will perform a detailed review and interpret these findings from the perspective of a healthcare value framework within the setting of the current relevant literature.

Study Setting

Department of Radiation Oncology at the University of Texas MD Anderson Cancer Center (Houston, Texas)

Study Subjects

Patients treated at MD Anderson with radiation therapy from January 1, 2010 to November 30, 2018 were included. All patients who received treatment and died within 6 months of starting radiation, including patients treated with definitive (curative) intent and patients who received palliative treatment, were included in the analysis.

Sample Size Calculation and/or Study Power

There was no formally calculated sample size given the retrospective nature of this review. We sought to capture the overall experience of treated patients at our institution. However, initial review of the total dataset indicated that several hundred patients met the eligibility criteria within the wide timeframe and were included in the analysis. Despite its retrospective nature, these patient numbers increased the likelihood of finding meaningful and statistically-significant findings.

Data Collection

This study was IRB-approved by the University of Texas MD Anderson Cancer Center (PA15-0639). For each identified patient, a retrospective chart review was conducted within the electronic medical records (EPIC/OneConnect and ClinicStation) for various clinical variables and mortality.

Data Analysis

Once the cohort was established, individual clinical variables (e.g. age, race, diagnosis, treatment site, hospitalization status, etc.) were analyzed and used to determine if there was an ability to predict mortality during or after radiation therapy. Regarding statistical analyses, we applied logistic regression techniques to determine the factors that predispose to mortality after radiation therapy via associations of outcome to patient and treatment characteristics. These data can help guide clinical practice guidelines which will be developed following review of the data by an expert provider panel including the principal investigator.

Human Subjects and Safety Considerations

This protocol is a retrospective study which was IRB-approved by the University of Texas MD Anderson Cancer Center (PA15-0639), including approval of a waiver of informed consent, given the retrospective nature of this project. This protocol was

also approved by the University of Texas Health Science Center Committee for Protection of Human Subjects (HSC-SPH-18-1068).

Patient confidentiality was strictly maintained. The research involved no more than minimal risk to the study subjects (i.e. risk of accidental release of personal and or confidential information) because the patient history and treatment details of these deceased patients were gathered from the hospital records. The waiver or alteration did not adversely affect the rights, welfare, or subsequent clinical management. This research could not practically be carried out without the waiver or alteration, given that study subjects are deceased.

Cases were coded by anonymous study number using a key kept separate from the database. Only the principal investigator of this study had access to patient information, and only information relevant to this protocol was examined. All protected health information was de-identified prior to releasing outcomes of the study outside the research team. Strict patient confidentiality was maintained.

Data was stored on a password and firewall protected computer. A study identifier was assigned to each case. A separate file containing the identifier and subject names/MRN was maintained. Data was presented in aggregate. Data was solely available to the principal investigator working on the project and kept on a password-protected hard-drive with no patient specific information.

There are no paper records of data with personal identifiers. Patient identifiers will be destroyed within 5 years of study completion. Until then, the database will be

password protected on a limited access computer. Information will be destroyed within 5 years after study publication.

JOURNAL ARTICLE

Predictors of On-Treatment and 30-Day Post-Treatment Mortality in Palliative Radiation Therapy: Improving the Quality of End-of-Life Cancer Care

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Matthew S. Ning[1], Prajnan Das[1], Ann H. Klopp[1], Daniel R. Gomez[1], Zhongxing Liao[1], Joe Y. Chang[1], Bouthaina S. Dabaja[1], Paige L. Nitsch[2], Rachel B. Natter[1], Pamela K. Allen[1], Tina M. Briere[2], Rebecca Wells[3], Joseph M. Herman[1], Albert C. Koong[1], and Mary F. McAleer[1]

[1]Department of Radiation Oncology and [2]Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]Department of Management, Policy, and Community Health, University of Texas Health Science Center School of Public Health

***Corresponding author**: Mary F. McAleer, MD, PhD; Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Unit 0097, 1515 Holcombe Blvd., Houston, TX 77030; Tel 713-563-2370; e-mail: mfmcalee@mdanderson.org

ABSTRACT

PURPOSE: Excessive medical treatment at end-of-life is an indicator of poor-quality care. While radiation therapy (RT) is effective for palliation, some patients die shortly after or even during treatment. Any treatment requiring terminal patients to spend significant time in the hospital contradicts palliative goals. This study investigates patterns of end-of-life RT at our institution to inform practice guidelines and quality improvement initiatives.

MATERIALS AND METHODS: All patients who died within 6 months of starting RT at our large academic cancer center between 2015 through 2018 were identified. Clinical factors including age, diagnosis, inpatient status, number of fractions, treatment date, service, and site were evaluated for associations with endpoints, 30-day mortality and on-treatment (mid-course) mortality, via logistic regression.

RESULTS: A total of 1,855 patients died within 6 months of initiating RT. Of these, 619 died within 30 days, and were most commonly treated by thoracic (26%), CNS (21%), and hematologic (13%) services. Commonly treated sites included brain/spine (27%), bone (26%), and mediastinum/thorax (10%). Both extended fractionation (>10/course) [OR 0.50, $p<0.001$] and stereotactic technique (OR 0.61, $p=0.002$) were associated with decreased 30-day mortality, reflecting clinical rationale of providers. Neither age (≥70 vs. <70 years) [$p=0.538$] nor treatment year (2017-2018 vs. 2015-2016) [$p=0.744$] were associated with 30-day mortality. Of 619 patients, 142 (23%) died mid-course before completion. Patients treated for

emergent mediastinal/thoracic indications (OR 11.4, $p<0.001$) were more likely to die mid-course than those treated for bone metastases. Notably, 2 of every 3 patients treated for emergent mediastinal/thoracic indications died on-treatment, comprising 27% of on-treatment deaths ($p<0.001$).

CONCLUSION: Palliative RT remains an important therapeutic tool at the end-of-life. However, careful consideration of RT for emergent mediastinal/thoracic indications should be used, given high potential for on-treatment mortality. Taken together, these data help inform physician decision-making and facilitate treatment consistent with palliative goals.

INTRODUCTION

Radiation therapy is an effective tool for palliation of symptoms arising from cancer—such as pain from bone metastases [1,2], neurologic compromise from spine or brain metastases [3], or bleeding from tumors [4]—and thus serves as an important mainstay of end-of-life oncologic care. However, while RT is effective for palliation, some patients may die during treatment, or too shortly afterwards to realize palliative benefit; and any therapy requiring terminal patients to spend significant time in the hospital contradicts palliative goals.

Excessive medical treatment at the end-of-life is an indicator of poor-quality care [5,6], yet many patients continue to receive aggressive treatment in their last days [7,8]. Along these lines, recent practice patterns for palliative RT have been examined with scrutiny due to concerns for overutilization. An estimated 1 in 5 patients who receive RT in their final 30 days of life will spend >10 of those days receiving treatment [5]; and among these patients, there has also been a shift towards more advanced RT technologies, away from simpler (and more cost-effective) techniques [9,10].

Much of this overutilization likely stems from the difficulty of accurately predicting life expectancies for terminally ill patients. Physicians tend to misjudge patient survival times [11–16], which can lead to overtreatment or extended treatment courses disproportionate to patient life expectancies. Taken together,

these practice trends call for more data to facilitate physician decision-making at the end-of-life and improve the quality of palliative RT.

To help address this literature void, our study investigates the patterns of on-treatment and early post-treatment mortality for palliative RT at our large academic cancer center. This investigation is the largest of its kind to date—encompassing all tumor histologies, disease sites, and palliative indications—and thus improves upon limited prior reports [17–19]. In addition to describing these patterns, we evaluate specific clinical factors associated with early post-treatment and on-treatment mortality, to inform subsequent practice guidelines and quality improvement initiatives.

MATERIALS AND METHODS

Design, Patient Population, and Data Sources

All patients who died within 6 months of starting RT at a single large academic cancer center between January 1, 2015 through December 31, 2018 were identified through our institutional databases. Various clinical factors including age, treatment service, number of fractions, diagnosis, treatment site, indication, inpatient status, and treatment date were collected. This study protocol was approved by the Institutional Review Board at the University of Texas MD Anderson Cancer Center (PA15-0639).

Statistical Analyses

The primary endpoints were on-treatment (mid-course) mortality and 30-day (early) post-treatment mortality (computed from the start of RT). Univariate and multivariable logistic regression analyses were conducted to identify potential associations between clinical or treatment variables and mortality endpoints, generating odds ratios (ORs) and 95% confidence intervals (CIs). Statistical analyses were performed in SPSS version 23 (IBM Corp, release 2015; IBM SPSS Statistics for Windows, Version 23.0; Armonk, NY: IBM Corp). For all statistical tests, a p-value <0.05 was considered significant.

RESULTS

Patient and Treatment Characteristics

A total of 1,855 patients died within 6 months of initiating RT at our center. Of these, 619 patients (33%) died within 30 days of starting RT, and were most commonly treated by thoracic (26%), CNS (21%), and hematologic (13%) services. Commonly treated sites included brain/spine (27%), bone (26%), and mediastinum/thorax (10%). Roughly 20% of hematologic patients were stem cell transplant candidates.

Factors Associated with Mortality within 30 Days of RT

On logistic regression, both extended radiotherapy prescription fractionation (>10 fractions/course) [OR 0.50, p<0.001] and advanced stereotactic treatment technique

(OR 0.61, p=0.002) were associated with decreased likelihood of 30-day mortality, reflecting appropriate clinical rationale of treating providers. Neither age (≥70 vs. <70 years) [OR 0.93, p=0.538] nor treatment year (2017-2018 vs. 2015-2016) [OR 0.97, p=0.744] were associated with 30-day mortality.

Factors Associated with On-Treatment Mortality During RT

Of the 619 patients, 142 (23%) died midway before completion of RT course. Patients treated for emergent palliative mediastinal/thoracic indications (OR 11.4, p<0.001) were more likely to die midway through RT than those treated for bone metastases. Notably, 2 out of every 3 patients treated for emergent palliative mediastinal/thoracic indications (e.g. airway obstruction, hemoptysis) died on-treatment, comprising 27% of all on-treatment deaths (p<0.001). Of note, 80% of all patients who died on-treatment were inpatients, while 82% of the thoracic/mediastinum patients were inpatient.

DISCUSSION

In this study investigating patterns of mid-treatment and early post-treatment mortality in palliative RT, our pertinent findings were as follows: (a) out of all patients who died within 6 months of initiating RT at our institution, one-third died within the first 30 days following RT, and a quarter of those patients died on-treatment; (b) inpatient status was significantly associated with mid-course mortality, with 80% of

on-treatment deaths occurring in hospitalized patients; and finally (c) patients treated for emergent mediastinal/thoracic indications were more likely to die on treatment, with 2 of every 3 patients dying before completion of RT.

The high proportion of patients dying shortly after or even during palliative RT at our institution is consistent with prior reports of RT utilization at the end-of-life [5,17]. This discrepancy likely stems from provider tendency to overestimate survival times for terminally ill patients, which leads to difficulty in tailoring palliative regimens appropriately to limited life expectancies [11–16]. As such, these data call for additional efforts focused on improving life expectancy assessments. Reassuringly, our study demonstrated lower utilization of extended fraction prescriptions (>10 fractions/course) and advanced stereotactic techniques in patients who died within 30 days of RT. This finding is consistent with the ASTRO Choosing Wisely guidelines for end-of-life treatment, which advocate for shorter palliative courses for patients with limited prognoses, as multiple studies have demonstrated the non-inferiority of shorter regimens [2,20,21].

With regard to clinical prognostic factors, inpatient hospitalization status during RT was significantly associated with on-treatment mortality among our patient population. This finding is corroborated by prior reports of palliative RT which demonstrate worse survival outcomes for patients evaluated as inpatient consults [17,22], and for those with advanced disease experiencing an unplanned admission for symptom control [18] or an intensive care unit admission [19]. Similarly, Grade et

al. similarly demonstrated higher rates of stopping treatment early among inpatients [18]. Taken together, these data support inpatient RT as a clinical prompt for comprehensive palliative care and hospice referral, if not already present. Shorter hypo-fractionated treatment courses are also preferred in this setting, given the poor performance statuses and prognoses of such inpatients.

In addition to inpatient status, our study found emergent mediastinal/thoracic indications to be highly associated with on-treatment mortality, with 2 out of every 3 patients dying before completion of RT. In general, many patients with metastatic or incurable locally advanced lung cancers can benefit from palliative thoracic RT to alleviate tumor-related symptoms such as hemoptysis, cough, and chest pain [23–26]; and even high-dose rate endobronchial brachytherapy is efficacious for palliating airway obstruction or hemoptysis due to endobronchial tumors [25,27]. However, our data indicate that the majority of *emergent* mediastinal/thoracic cases (e.g. severe hemoptysis or bronchial obstruction in the inpatient setting) are likely to die mid-treatment prior to RT completion. These findings are consistent with those of Grade et al., who demonstrated airway compromise as a serious indication associated with worse survival [18]. Therefore, while palliative RT can be safe and efficacious for a range of thoracic indications, providers should exercise caution for emergent mediastinal/thoracic cases, given the high likelihood of on-treatment mortality in this setting.

To summarize, this study analyzes the patterns of on-treatment and early post-treatment mortality of patients undergoing palliative RT at a large academic cancer center. The major limitation of this work is its single-institution, retrospective nature, reflecting practice patterns specific to our provider group. However, our study benefits from being the largest series of its kind to date and encompassing a wide range of palliative indications and sites, thereby improving upon previous reports [17–19]. Taken together, these data can inform practice guidelines and quality improvement initiatives aimed at optimizing end-of-life care for terminally-ill patients with cancer.

CONCLUSION

To summarize, this study analyzes the patterns of on-treatment and early post-treatment mortality of patients undergoing palliative RT at a large academic cancer center. Palliative RT remains an important therapeutic tool at the end-of-life. However, careful consideration of RT for emergent mediastinal/thoracic indications should be used, given the high potential for on-treatment mortality. Taken together, these data may help inform physician decision-making and facilitate treatment consistent with palliative goals at the end-of-life.

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